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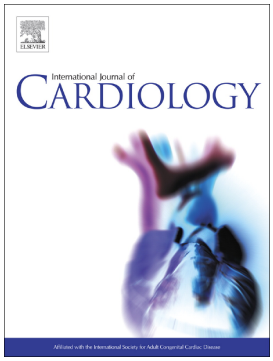

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Stroke, thromboembolism and bleeding in patients with atrial fibrillation according to the EHRA valvular heart disease classification

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Abstract

Aims. We compared thromboembolic (TE) and bleeding risks in patients with atrial fibrillation (AF) according to the new '**E**valuated **H**eartvalves, **R**heumatic or **A**rtificial' (EHRA) valve classification.

Methods Patients were divided into 3 categories: (i) EHRA type 1 corresponds to the previous 'valvular' AF patients, with either rheumatic mitral valve stenosis or mechanical prosthetic heart valves; (ii) EHRA type 2 includes AF patients with other valvular heart disease (VHD) and valve bioprosthesis or repair; and (iii) 'non-VHD controls' i.e. all AF patients with neither VHD nor post-surgical valve disease.

Results Among 8962 AF patients seen between 2000 and 2010, 357 (4%) were EHRA type 1, 1,754 (20%) were EHRA type 2 and 6,851 (76%) non-VHD controls. EHRA type 2 patients were older and had a higher CHA_2DS_2-VASc and HAS-BLED scores than either type 1 and non-VHD patients. After a mean follow-up of 1,264±1,160 days, the occurrence of TE events was higher in EHRA type 2 than non-VHD patients (HR (95%CI): 1.30 1.09-1.54), p=0.003; also, p=0.31 for type 1 vs 2, p=0.68 for type 1 vs non-VHD controls). The rate of major BARC bleeding events for AF patients was higher in either EHRA type 1 (HR (95%CI): 3.16(2.11-4.72), p<0.0001) or type 2 (HR (95%CI): 2.19(1.69-2.84), p<0.0001) compared to non-VHD controls.

Conclusion The EHRA valve classification of AF patients with VHD appears useful in categorizing these patients, in terms of TE and bleeding risks. This classification can be used in clinical practice for appropriate choices of oral anticoagulation therapy and follow-up.

Key words: atrial fibrillation, ischemic stroke, valvular heart disease, valve prosthesis.

INTRODUCTION

Atrial fibrillation (AF) confers a substantial risk of fatal and disabling stroke and randomized trials have conclusively demonstrated that oral anticoagulation (OAC) reduces the risk of stroke/systemic embolism and all-cause mortality [1]. Valvular heart disease (VHD) is frequently (approximately 30%) and independently associated with incident AF [2]. Such AF patients have been traditionally been dichotomized as 'non valvular' AF or 'valvular' AF [1,3], but different definitions have been used in clinical practice, guidelines and research studies, leading to possible confusion [4,5].

The term of 'valvular AF' usually applies to patients with AF associated with moderate-severe mitral stenosis of rheumatic origin or to mechanical prosthetic valve replacements. These patients have a high TE risk even in sinus rhythm, which is even higher in case of associated AF, such that these patients require chronic OAC with VKA irrespective of their CHA_2DS_2-VASc score [1,6,7]. In 'non valvular' AF, guidelines recommended OAC use (ie. a Vitamin K Antagonist (VKA) or a NOAC), provided that the CHA_2DS_2-VASc score is $\geq$1 in males and $\geq$2 in females [1,8]. Of note, there is an increased embolic risk in 'non-valvular AF' patients with VHDs other than severe mitral stenosis or mechanical prosthetic valves, compared with those with no VHD [9]. For example, AF patients with valvular bioprosthesis have a higher TE risk than those with 'non-valvular' AF and the CHA_2DS_2VASc score (derived from 'non-valvular AF') is useful for TE risk prediction [10].

How best to treat such patients? Despite the absence of robust data, non-VKA oral anticoagulants (NOACs) has been proposed in patients who have AF associated with an aortic bioprosthesis >3months after implantation [15,16]. Indeed, recent subgroup analyses of randomized trials on AF support the use of NOACs in AF patients with aortic stenosis, aortic regurgitation or mitral regurgitation [11–14].

When asked about the 'valvular/non valvular' AF definition, physicians have important uncertainties in their answers given the lack of a clear and accepted definition [5,17]. Recently, the '**E**valuated **H**eartvalves, **R**heumatic or **A**rtificial' (EHRA) classification has been proposed for AF

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patients with VHD [7]. The latter are categorized as EHRA type 1 which correspond to the current 'valvular' AF patients; or EHRA type 2 that includes other VHD AF patients and post-surgical valve disease including valve repair, bioprosthesis, TAVI and Mitraclip. The aim of the present study was to compare thromboembolic risk in AF patients according to their EHRA valve classification status and secondly, to evaluate whether this classification would be more clinically relevant than the previous 'valvular/non valvular' AF definitions.

METHODS

Study population

We included all patients with a diagnosis of AF seen in the cardiology department in our institution between January 2000 and December 2010. Patients' characteristics were obtained from the records of our institution's computerized codification system for each patient [9,10]. Patients with post-surgical AF only were not included in the study. Patients were divided into 3 categories according to the EHRA valve classification, as follows: (i) **EHRA type 1 VHD** corresponds to the current 'valvular' AF patients which includes those with either rheumatic mitral valve stenosis or mechanical valvular prosthesis [1]; (ii) **EHRA type 2 VHD** includes other VHD AF patients, valve repair, bioprosthesis, TAVI and Mitraclip; and (iii) non-VHD controls correspond to all AF patients without any VHD nor valvular prosthesis or repair. The CHA_2DS_2-VASc score, which has been validated in 'non valvular AF', and HAS-BLED score were calculated for each patient. VKA therapy was the only form of OAC used during the study period.

Data on death and events during follow-up until December 2010 were obtained by searching in the medical database from consultation and hospitalization reports. The Regional University Hospital Centre (CHRU) of Tours serves approximately 400,000 inhabitants, is the only public institution in an area of about 4,000 km² and includes a total of 4 hospitals covering all medical and surgical specialties. We defined major bleeding using the Bleeding Academic Research Consortium (BARC) definitions [18]. Major BARC bleeding was defined as bleeding with a reduction in the

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hemoglobin level of at least 20 g per litre, or with transfusion of at least 1 unit of blood, or symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) or bleeding that causes death [18].

The study was approved by the institutional review board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital, on December 7, 2010 and registered as a clinical audit. Ethical review was therefore not required and patient consent was not sought. The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care.

Statistical analysis

Comparisons between groups were made using chi-square tests to compare categorical variables, and the Student t test or the non-parametric Kruskal Wallis test where appropriate for continuous variables. A proportional hazard model was used to identify independent characteristics associated with the occurrence of an event during follow-up. The proportional hazard assumption was checked by plotting the log-log Kaplan Meier curves. The results were expressed as hazard ratios (HR) and 95% confidence intervals (CI). Harrell's c-statistic with 95% CIs was calculated as a measure of model performance. The CHA_2DS_2-VASc score was analysed as a continuous variable and as a categorical variable (low CHA_2DS_2-VASc risk if 0 in males or 1 in females, moderate if 1 in males and 2 in females, and high if >1 in males and >2 in females). The C statistics were compared using the DeLong test. A p value <0.05 was considered statistically significant. Statview 5.0 (Abacus, Berkeley CA, USA), Medcalc 15.2 (MedCalc Software, Mariakerke, Belgium) and JMP ® 9.0.1 (SAS Institute, Cary, NC, USA) were used for statistical analysis.

RESULTS

A total of 8,962 patients suffering from AF were included in this study (Supplemental figure 1). True 'valvular' AF patients corresponding to EHRA type 1 was present in 357 (4%), consisting of 124 with mitral stenosis and 243 mechanical valve prosthesis. For the 'non valvular' AF patients, 1,754 (20%) belonged to EHRA type 2 and 6,851 (76%) were non-VHD controls. The characteristics of these patients are shown in Table 1.

Non-VHD control AF patients were younger, more frequently women and were more prone to have permanent AF than other patients. EHRA type 2 patients were older and had more heart failure, coronary artery disease and previous myocardial infarction, hypertension, renal insufficiency, diabetes mellitus, and hyperlipidaemia than EHRA type 1 and non-VHD controls. Thus, the average CHA_2DS_2-VASc and HAS-BLED scores in EHRA type 2 patients were higher. Concerning medical therapies, type 1 AF patients more frequently received OAC (78%) and type 2 were more commonly treated with angiotensin converting enzyme (ACE) or angiotensin 2-blocker (47%), beta-blockers (45%) and diuretics (62%).

Thromboembolic events

The mean follow-up period was 1,264±1,160 days (median 922 days, interquartile range 234-2,083), and there were 715 TE events. The rate of TE events for AF patients was significantly higher (1.30 (95%CI: 1.09-1.54), p=0.003) in EHRA type 2 than non-VHD controls (p=0.012 for overall Log rank test; p=0.31 for type 1 *vs* 2, p=0.68 for type 1 *vs* non-VHD controls) (figure 1). After adjustment for age, gender and anticoagulant use, there was no significant differences between the 3 groups. Increasing age and CHA_2DS_2-VASc score were independently associated with an increased risk of TE events (Supplemental table 2). Oral anticoagulation and female gender were independently associated with a lower risk of TE events. Distinguishing patients according to the EHRA valve classification among type 2 and non-VHD controls was not an independent predictor of TE events after adjustment for confounding factors.

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Using c-statistics, we measured the performance of the CHA_2DS_2-VASc score in the VHD patients (Table 2). The CHA_2DS_2-VASc score as continuous variable significantly better predicted TE risk in non-VHD controls compared to EHRA type 2 patients in the non-anticoagulated sub-group, with a similar finding in the overall AF population. Prediction was non-significantly different between EHRA type 1 and type 2 patients (except for non-anticoagulated patients when analysed as continuous variable) nor between type 1 and non-VHD controls.

In supplemental table 1, a modelling analysis, based on metaanalysis by Ruff et al [19], would show the added advantage of NOACs in reducing event rates in moderate-high risk patients based on the CHA_2DS_2-VASc score. In addition, the CHA_2DS_2-VASc score performed similarly well in identifying 'low risk' patients whether the AF patients was EHRA type 2 or non-VHD controls. Increasing age and CHA2DS2-VASc score were independently associated with an increased risk of TE events (Supplemental table 2).

Bleeding events

The rate of major BARC bleeding events for AF patients was different according to the EHRA type ($p<0.0001$ for the overall Log rank test, $p=0.10$ for type 1 *vs* 2, $p<0.0001$ for type 1 *vs* non-VHD controls and $p<0.0001$ for type 2 *vs* non-VHD controls) (figure 1). After adjustment for age, gender, antiplatelet therapy (APT) and anticoagulant use, type 1 and type 2 patients respectively had a 2.73 (95% CI: 1.72-4.31, $p<0.0001$) and 2.05 (95% CI: 1.55-2.70, $p<0.0001$) fold increased risk of major BARC bleeding than non-VHD patients. There was no difference between type 1 and 2 after adjustment for confounding factors.

C-statistics for the HAS-BLED score showed better prediction of major BARC bleeding in non-VHD controls *vs* type 2, and type 2 *vs* type 1 in the overall population (table 3). In patients on VKA, the area under the curve (AUC) for non-VHD patients was significantly higher than the other patient groups. Supplemental table 3 shows major bleeding annual rates for each of the study groups.

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DISCUSSION

In this study, we have shown that dividing the AF population according to the new EHRA classification for valvular AF allows differentiation of different risk profiles. Specifically, EHRA type 2 patients, now corresponding to AF patients with VHD or valve repair, had a higher TE risk than non-VHD control patients (ie. 'non valvular' AF patient without any valve disease or surgery). Second, a higher CHA_2DS_2-VASc score was likely to explain the increased risk in these AF patients with VHD.

In our cohort, 20% were EHRA type 2 AF patients, and these were generally pooled with non-VHD AF patients in the older definitions of the 'non valvular' AF group. Indeed, the higher TE risk of EHRA type 2 patients can be attributable to an older age and more frequent comorbidities, de facto increasing the CHA_2DS_2-VASc score. These observations have previously been reported with a significant difference for TE risk in VHD and only a trend for bioprosthesis [9,10]. EHRA Type 1 patients corresponding to 'valvular' AF had a non-significant TE risk when compared to type 2 and non-VHD controls, partly related to the higher rate of OAC use, reaching 78%.

Increasing age and CHA_2DS_2-VASc score were the main variables that were independent predictors of TE events. Although the predictive value of the CHA_2DS_2-VASc score was lower in type 2 *vs* non-VHD controls in non-anticoagulated patients (and *vs* type 1) in contrast to previous studies [9,10], the score performed well in identifying 'low risk' patients in all groups. 'Low risk' patients had a low rate of TE events regardless of their AF type and OAC was not associated with any benefit in this setting. There was underuse of anticoagulation in the EHRA type 1 group, where all should ideally be on anticoagulation. This might be related to prior bleeding, severe comorbidities or paroxysmal AF of short duration in some patients.

OAC is generally recommended when the yearly rate of TE events is expected to be above 1% for patients with a so-called 'non-valvular' AF [1]. Our results suggest that no OAC might be

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acceptable in these patients (EHRA type 2 and non-VHD patients) at low-risk of TE events, particularly when they have a high HAS-BLED score and/or when bleeding events are documented with OAC.

Major bleeding risk was significantly higher in type 1 and 2 *vs* non-VHD control patients, and the higher rate of anticoagulant prescription may in part explain this result. Once adjusted for antiplatelet therapy and VKA use, the risk of major bleeding events was still 2-fold higher in type 2 *vs* non-VHD controls. Whether the differences in bleeding events are a play of chance, are a true biological effect, or reflect unidentified confounding effects (e.g. differences in practice patterns) remain uncertain. Patients with VHD more frequently had higher HAS-BLED score and/or OAC during the course of the study and this would be possible explanations even after adjustment. The higher incidence of major bleeding events in type 2 *vs* non-VHD control patients has already been observed in patients taking NOACs in subgroup analyses of randomized trials [11–13]. The presence of any VHD or post-surgical valve disease did not influence the comparison of NOAC with warfarin in these trials, with a lower risk of bleeding events also found in "real life" data [20], except for Rivaroxaban which was the only NOAC associated with a higher risk of bleeding than VKA in such patients [11]. Nevertheless, he use of NOACs is discouraged in patients who have AF associated with mitral stenosis and strictly contraindicated with any mechanical prostheses (with Grade IIIC and IIIB recommendations, respectively) given their particularly high thromboembolic risk [1,6]. Indeed, the negative experience with dabigatran etexilate has halted the investigation of other NOACs (eg. FXa inhibitors) in such patients [21].

Limitations

This study was based on a registry and is subject to the limitations inherent to retrospective observational analyses. The study population was hospital-based and therefore may not be representative of all patients with AF. The study was not ethnically diverse and our findings may

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not be generalizable to other populations. Another caveat is that we did not have access to data on events occurring outside of our area. There were also numerous variables to be taken into account, and it is possible that we had overlooked confounding factors, which might affect the value of multivariable statistical analysis. Otherwise, as our study extends from 2000 to 2010, and patients were not yet taking NOACs. Without any such patients, we only made assumptive projections for NOACs whereas the others were based upon observation. Finally, we had access neither to precise variations in antithrombotic treatment during follow-up, nor to levels of anticoagulation by serial measurements of the INR, a common limitation in such 'real life' observational analysis.

CONCLUSION

The EHRA valve classification of AF patients with VHD appears useful in categorizing these patients, in terms of TE and bleeding risks. This classification can be used in clinical practice for appropriate choices of OAC therapy and follow-up.

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NC has served as a consultant or speaker for Boston Scientific and Medtronic. DB has been on the speakers bureau from BMS/Pfizer and Medtronic. GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are received personally. LF has served as a consultant or speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Livanova, Medtronic and Novartis. Other authors - no conflicts of interest.

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Figure legends

Figure 1. Top panel: Stroke and/or thromboembolic events in patients with atrial fibrillation according to the EHRA valve classification status. Lower panel: Major BARC bleeding events in patients with atrial fibrillation according to the EHRA valve classification status.

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Table 1. Characteristics of the patients with AF according to EHRA valve classification

Variable	EHRA Type 1 n= 357(4%)	EHRA Type 2 n= 1,754(20%)	EHRA Non-VHD n= 6,851(76%)	p
Age (years) (mean±SD)	68±13	75±11	70±15	<0.0001
Women	198(55%)	704(40%)	2,565(37%)	<0.0001
Heart failure	243(68%)	1,281(73%)	3,388(49%)	<0.0001
Coronary artery disease	86(24%)	609(35%)	2,023(30%)	<0.0001
Previous myocardial infarction	24(7%)	295(17%)	979(14%)	<0.0001
Pacemaker or implantable cardioverter defibrillator	77(22%)	325(19%)	1,130(16%)	0.009
Hypertension	97(27%)	785(45%)	2,861(42%)	<0.0001
Previous ischaemic stroke	32(9%)	142(8%)	564(8%)	0.86
Renal insufficiency	46(13%)	240(14%)	522(8%)	<0.0001
Diabetes mellitus	51(14%)	300(17%)	1,058(15%)	0.18
Chronic obstructive pulmonary disease	42(12%)	206(12%)	703(10%)	0.15
Hyperlipidaemia	65(18%)	395(23%)	1,304(19%)	0.004
Permanent atrial fibrillation	205(57%)	850(48%)	2,440(36%)	<0.0001
CHA_2DS_2VASc score (mean±SD)	3±1.7	3.6±1.6	2.9±1.8	<0.0001
HASBLED score (mean±SD)	1.4±1.1	1.9±1.1	1.5±1.1	<0.0001
Left ventricular ejection fraction (mean±SD) (n=1,934)	53±17	48±16	46±16	<0.0001
Left ventricular ejection fraction ≤45 % (n=1,934)	36(31%)	298(46%)	552(47%)	0.005
Medication during follow-up				
Oral anticoagulation (n=8,120)	258(78%)	971(61%)	3,408(55%)	<0.0001
Antiplatelet therapy (n=7,969)	56(17%)	529(34%)	2,095(34%)	<0.0001
Angiotensin converting enzyme inhibitor or Angiotensin 2-blocker (n=8,671)	134(38%)	809(47%)	2,106(32%)	<0.0001
Beta-blocker (n=8,767)	152(44%)	778(45%)	2,976(44%)	0.84
Diuretic (n=8,224)	203(60%)	1,033(62%)	2,122(34%)	<0.0001
Digoxine (n=8,871)	149(42%)	570(33%)	1,440(21%)	<0.0001
Class III antiarrhythmic agent (n=8,862)	156(44%)	783(45%)	2,754(41%)	0.003

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Table 2. Comparison of c-statistics (95% confidence intervals) for CHA_2DS_2VASc scoring system according to EHRA valve classification type patients with atrial fibrillation

	C statistic (95% CI)[a]			
	EHRA Type 1	**EHRA Type 2**	**EHRA Non-VHD**	**p value Type 2 *vs* Non-VHD**
CHA_2DS_2VASc as a continuous variable				
All patients	(n=329)	(n=1,598)	(n=6,193)	0.05
	0.657(0.606-0.708)	0.629(0.605-0.653)[c]	0.655(0.643-0.667)[c]	
Patients not on VKA	(n=71)	(n=627)	(n=2,785)	<0.0001
	0.729(0.616-0.819)	0.577(0.538-0.615)[b]	0.666(0.648-0.683)[c]	
Patients on VKA	(n=258)	(n=971)	(n=3,408)	0.39
	0.630(0.570-0.687)	0.661(0.630-0.690)[c]	0.646(0.630-662)[c]	
CHA_2DS_2VASc as a categorical variable (low, moderate or high risk)				
All patients	(n=329)	(n=1,598)	(n=6,193)	<0.0001
	0.591(0.538-0.644)	0.534(0.510-0.558)[c]	0.601(0.589-0.613)[c]	
Patients not on VKA	(n=71)	(n=627)	(n=2,785)	<0.0001
	0.595(0.479-0.701)	0.512(0.473-0.551)[c]	0.624(0.606-0.642)[c]	
Patients on VKA	(n=258)	(n=971)	(n=3,408)	0.0524
	0.587(0.526-0.645)	0.547(0.516-0.578)[c]	0.582(0.565-0.599)[c]	

[a] C-statistic calculated as area-under-the-curve for the receiver-operator characteristic (ROC)
[b] $p<0.05$ *vs* type 1
[c] NS *vs* type 1

Table 3. Comparison of c-statistics (95% confidence intervals) for identifying the risk of major BARC bleeding events using the HASBLED scoring system according to EHRA valve classification type patients with atrial fibrillation.

	C statistic (95% CI)[a]			
	EHRA Type 1	**EHRA Type 2**	**EHRA Non-VHD**	**p value type 2 *vs* Non-VHD**
HASBLED as a continuous variable				
All patients	(n=329)	(n=1,598)	(n=6,193)	<0.0001
	0.505(0.451-0.559)	0.574(0.550-0.598)[b]	0.645(0.633-0.657)[b]	
Patients not on VKA	(n=71)	(n=627)	(n=2,785)	0.06
	0.641(0.529-0.753)	0.600(0.562-0.638)[c]	0.640(0.622-0.658)[c]	
Patients on VKA	(n=258)	(n=971)	(n=3,408)	0.0001
	0.545(0.484-0.606)	0.577(0.546-0.608)[c]	0.649(0.633-0.665)[b]	

[a] C-statistic calculated as area-under-the-curve for the receiver-operator characteristic (ROC)
[b] $p<0.05$ *vs* type 1
[c] NS *vs* type 1 or incalculable

Highlights

- A new definition of 'valvular/non-valvular' atrial fibrillation has been proposed.
- This new EHRA valve classification is clearer than the previous ones**.**
- It results in homogenous groups of patients for thromboembolic and bleeding risks.
- This classification should be useful in research for harmonization of studies.
- It may help daily practice for appropriate choices of anticoagulant and follow-up.

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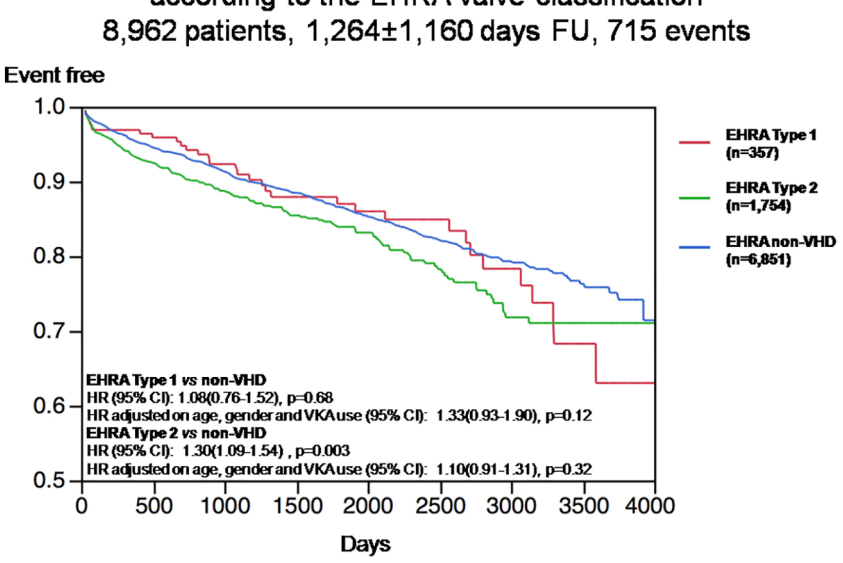

Stroke or systemic thromboembolism in AF patients
according to the EHRA valve classification
8,962 patients, 1,264±1,160 days FU, 715 events
Event free
1.0
0.9
0.8
0.7
0.6
0.5
0
500
1000
1500
2000
2500
3000
3500
4000
Days
EHRA Type 1 (n=357)
EHRA Type 2 (n=1,754)
EHRA non-VHD (n=6,851)
EHRA Type 1 vs non-VHD
HR (95% CI): 1.08(0.76-1.52), p=0.68
HR adjusted on age, gender and VKA use (95% CI): 1.33(0.93-1.90), p=0.12
EHRA Type 2 vs non-VHD
HR (95% CI): 1.30(1.09-1.54) , p=0.003
HR adjusted on age, gender and VKA use (95% CI): 1.10(0.91-1.31), p=0.32

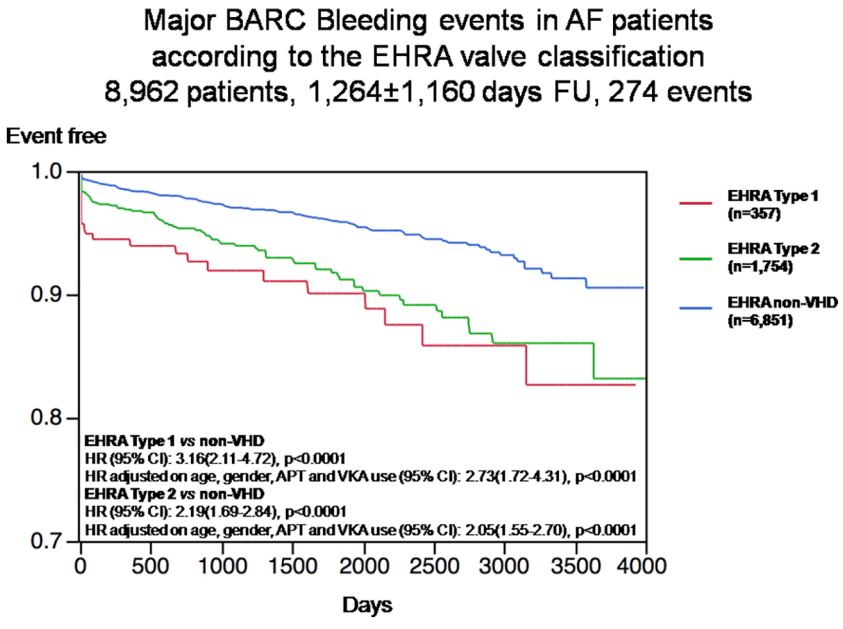
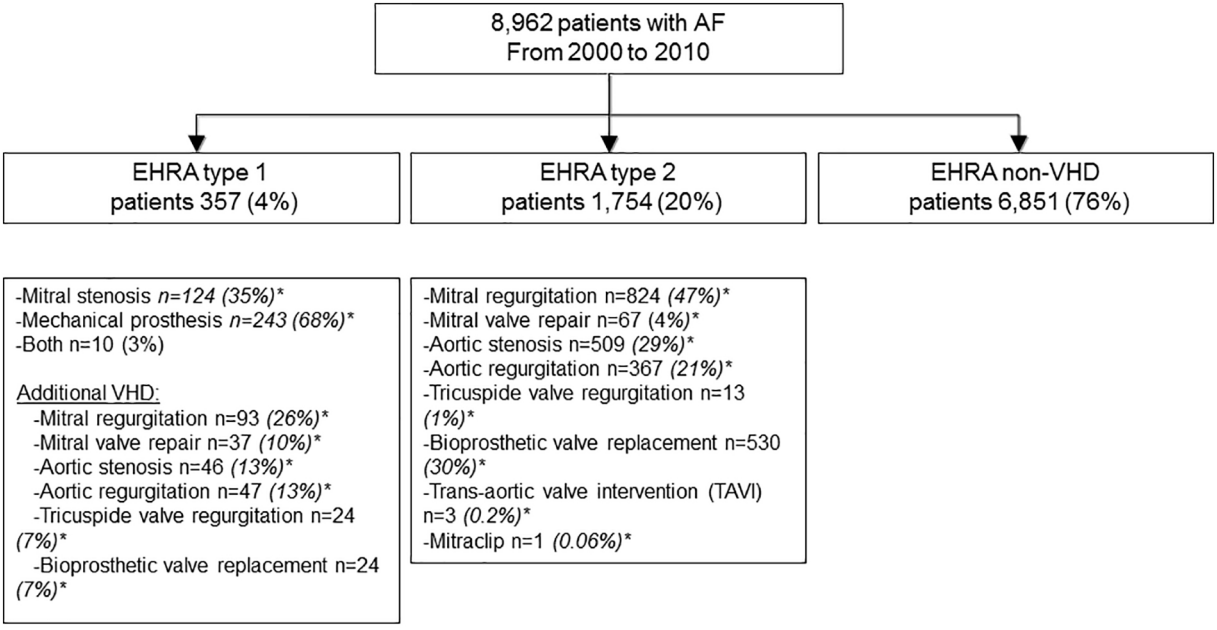

Major BARC Bleeding events in AF patients
according to the EHRA valve classification
8,962 patients, 1,264±1,160 days FU, 274 events
Event free
1.0
0.9
0.8
0.7
0
500
1000
1500
2000
2500
3000
3500
4000
Days
EHRA Type 1 (n=357)
EHRA Type 2 (n=1,754)
EHRA non-VHD (n=6,851)
EHRA Type 1 vs non-VHD
HR (95% CI): 3.16(2.11-4.72), p<0.0001
HR adjusted on age, gender, APT and VKA use (95% CI): 2.73(1.72-4.31), p<0.0001
EHRA Type 2 vs non-VHD
HR (95% CI): 2.19(1.69-2.84), p<0.0001
HR adjusted on age, gender, APT and VKA use (95% CI): 2.05(1.55-2.70), p<0.0001

Figure 1



** percent patients within each EHRA type*

Figure 2